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Pulmonary Metastases From Soft Tissue Sarcoma

Analysis of Patterns of Disease and Postmetastasis Survival

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Objective

To report the patterns of disease and postmetastasis survival for patients with pulmonary metastases from soft tissue sarcoma in a large group of patients treated at a single institution. Clinical factors that influence postmetastasis survival are analyzed.

Summary Background Data

For patients with soft tissue sarcoma, the lungs are the most common site of metastatic disease. Although pulmonary metastases most commonly arise from primary tumors in the extremities, they may arise from almost any primary site or histology. To date, resection of disease has been the only effective therapy for metastatic sarcoma.

Methods

From July 1982 to February 1997, 3149 adult patients with soft tissue sarcoma were admitted and treated at Memorial Sloan-Kettering Cancer Center. During this interval, 719 patients either developed or presented with lung metastases. Patients were treated with resection of metastatic disease whenever possible. Disease-specific survival was the endpoint of the study. Time to death was modeled using the method of Kaplan and Meier. The association of factors to time-to-event endpoints was analyzed using the log-rank test for univariate analysis and the Cox proportional hazards model for multivariate analysis.

Results

The overall median survival from diagnosis of pulmonary metastasis for all patients was 15 months. The 3-year actuarial survival rate was 25%. The ability to resect all metastatic disease completely was the most important prognostic factor for survival. Patients treated with complete resection had a median survival of 33 months and a 3-year actuarial survival rate of 46%. For patients treated with nonoperative therapy, the median survival was 11 months. A disease-free interval of more than 12 months before the development of metastases was also a favorable prognostic factor. Unfavorable factors included the histologic variants of liposarcoma and malignant peripheral nerve tumors and patient age older than 50 years at the time of treatment of metastasis.

Conclusions

Resection of metastatic disease is the single most important factor that determines outcome in these patients. Long-term survival is possible in selected patients, particularly when recurrent pulmonary disease is resected. Surgical excision should remain the treatment of choice for metastases of soft tissue sarcoma to the lung.

Soft tissue sarcoma is a rare neoplasm: there are approximately 6600 cases annually in the United States.[1] Sarcoma may arise virtually anywhere, but the extremity is the most common primary site. Despite progress in multimodality treatment, more than 4000 Americans will die each year of soft tissue sarcoma. The lungs are the most common sites of metastatic disease. Of patients with extremity sarcoma, approximately 20% will have isolated pulmonary metastatic disease at some point in the course of their disease.[2] Although pulmonary metastases most commonly arise from primary tumors in the extremities, they may arise from almost any histologic variant or primary site.[3]

There is evidence that surgical resection is the treatment of choice for pulmonary metastases from soft tissue sar-

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coma.[4–6] Three-year survival rates after complete resection range from 30% to 42%.[4] Chemotherapy has not been proven to increase survival after the resection of pulmonary metastasis.[7,8]

Several prognostic variables have been identified that are associated with favorable survival after pulmonary metastasectomy. Favorable factors include an extended disease-free interval, three or fewer pulmonary nodules, and a longer tumor doubling time.[9] The most consistent favorable prognostic factor is metastatic disease that is amenable to resection.[6,10,11] In a report from our institution, the number of pulmonary nodules was not a significant prognostic indicator if all disease was resectable.[2]

The relation between histology and frequency of pulmonary metastasis is not well defined. There is evidence that patients with extremity spindle cell sarcoma and extraskeletal osteosarcoma are more likely to develop pulmonary metastases.[3] In a series of 242 patients, those with tenosynovial sarcoma also had an increased incidence of pulmonary metastases.[12]

The aim of this study is to report the patterns of disease and postmetastasis survival for patients with pulmonary metastases from soft tissue sarcoma in a large group of patients treated at a single institution. Previous series, including work from our institution,[2] have focused on patients with pulmonary metastases treated with surgical resection. In the current study, we examine outcomes for all patients with pulmonary metastases, including patients with nonextremity primary sites and patients not treated with resection. Variables of site of origin of the primary lesion and underlying histopathology are analyzed for their influence on survival after the development of pulmonary metastasis. Survival analysis also includes additional variables of tumor grade, size, patient age, and resection.

MATERIALS AND METHODS

Patient Population

From July 1, 1982, to February 28, 1997, 3149 adult patients with soft tissue sarcoma were admitted and treated at Memorial Sloan-Kettering Cancer Center (MSKCC). All data were prospectively entered into the sarcoma database, and patients were followed per management protocol. During this interval, 719 of these patients either developed or presented with lung metastases. These patients comprise the study group for this report. The histopathologic diagnosis and grade for all patients was reviewed and confirmed by an attending pathologist at MSKCC. Tumor grade, size, and anatomic location were recorded in the prospective database.

During the initial evaluation and follow-up, standard chest radiographs were obtained. Patients at high risk for metastases were also evaluated with chest computed tomography (CT) scans. After therapy for the primary tumor, patients were evaluated at regular intervals with chest radiographs, physical examination, and chest CT scans when indicated. After pulmonary metastases developed, the extent of overall disease was determined by physical examination, laboratory tests, and clinically directed studies. For patients with extremity sarcoma, this evaluation involved an imaging study of the extremity (either a CT scan or magnetic resonance imaging). Patients with visceral or retroperitoneal primaries were followed with regular abdominal imaging studies (primarily CT scan).

When diagnosed with pulmonary metastases, patients were treated with surgical resection unless a contraindication existed. Contraindications to resection included unresectable lung disease, extensive involvement of the mediastinum or chest wall, unresectable metastatic disease outside the thorax, or unresectable local recurrence. Patients were also deemed ineligible for resection if they had significant comorbid disease or insufficient pulmonary function to tolerate resection of all pulmonary disease.

Operative approaches included posterolateral thoracotomy, median sternotomy, staged, bilateral, posterolateral thoracotomies, and clamshell thoracotomy (bilateral anterolateral thoracotomy). If during follow-up recurrent, resectable lung metastases developed, they were treated with repeat lung resection.

Many patients with pulmonary metastases were treated with chemotherapy at some point in their clinical course. We include both patients prospectively randomized in chemotherapy trials as well as those who were given standard-of-care treatment based on prognosis. Because inclusion of nonrandomized treatment-related variables in any of the analyses would be likely to confound the effects of other factors, we have elected to include only the effect of surgical resection in the analyses.

Statistical Analysis

Disease-specific survival was used as the endpoint of the study. Survival was calculated from the date of diagnosis of the pulmonary metastasis, or from the date of surgery for patients treated with resection. The time to death was modeled using the method of Kaplan and Meier.[13] Deaths that resulted from the disease were treated as an endpoint for disease-specific survival; all other deaths were treated as censored observations. The association of these factors to time-to-event endpoints was analyzed using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model.[14] The results of the Cox model analysis are reported with relative risks and 95% confidence intervals. In all statistical analyses, $p < 0.05$ was considered significant.

RESULTS

Patient Characteristics

During the time period under study, 719 patients either developed or presented with lung metastases. Four hundred

Table 1. 719 PATIENTS WITH PULMONARY METASTASES: DISEASE STATUS AT PRESENTATION TO MEMORIAL SLOAN-KETTERING CANCER CENTER

Primary Disease		Recurrent or Metastatic Disease			
Primary only	274	Local recurrence*	53		
Primary + metastasis	129	Local + metastasis†	44		
		Metastasis	219		
Total Primary	403	Total recurrent/Metastasis	316	Total	719

* Patients presenting with local recurrence, subsequently developing pulmonary metastases.
† Patients presenting with local recurrence and simultaneous pulmonary metastases.

three patients (56%) presented to MSKCC for the management of their primary disease site (Table 1). Of these patients, 274 presented with primary disease and later developed pulmonary metastases. One hundred twenty-nine patients presented with primary disease and synchronous metastases.

Three hundred sixteen (44%) patients had their primary disease managed elsewhere and came to MSKCC with locoregional recurrence, metastatic disease, or both (Table 1). Two hundred nineteen of these patients presented with metastatic disease. Fifty-three patients presented to MSKCC with a local recurrence and later developed pulmonary metastases, and 44 patients had simultaneous local recurrence and metastatic disease. There were 352 (49%) female and 367 male (51%) patients. Six hundred forty-five (90%) of the patients had high-grade sarcomas, and 71 (10%) were histologically classified as low-grade lesions. Three patients had primary lesions of unknown or indeterminate grade. The mean age was 49 years (range 15–88). The follow-up in this series was calculated from the date of the diagnosis of the metastasis or the surgical date for patients who underwent resection. The median overall follow-up was 9.7 months. The median follow-up for surviving patients at the time of analysis was 10.4 months.

Primary Location

Review of all patients with lung metastases treated at MSKCC (Table 2) demonstrates that primary tumors of the trunk and extremity are the source for the majority of lung metastases (65%). In these patients, there is a high incidence of pulmonary metastases among patients with visceral sarcoma. Gynecologic visceral sarcoma (uterine, cervix, ovarian) is associated with pulmonary metastases in 38%, and genitourinary visceral sarcoma is associated with pulmonary metastases in 23%. Primary lesions in the retroperitoneum metastasize to the lungs infrequently (9%). Thoracic (chest wall, mediastinum, heart, diaphragm) tumors have an intermediate propensity to develop pulmonary metastatic disease.

To minimize referral bias, the analysis was repeated examining only patients who had their primary disease treated at MSKCC (n = 403). This analysis confirms the prevalence of pulmonary metastasis from truncal and extremity sarcoma. However, review of primary cases demonstrates that pulmonary metastatic disease from visceral primary sites is actually rare. In this group of patients, lung disease developed in only 8% of patients with a primary tumor arising from one of the visceral locations.

Histology

Almost all the histologic variants of soft tissue sarcoma were represented among the patients with pulmonary metastases. Analysis of the distribution of primary histology and grade demonstrates that among patients that develop lung metastases, leiomyosarcoma is the most common histology (21%), followed by malignant fibrous histiocytoma (18%), liposarcoma (12%), and synovial sarcoma 14% (Table 3).

The incidence of pulmonary metastases within each histologic group correlates with the incidence of high-grade lesions within that group. Undifferentiated sarcomas have the highest percentage with lung metastases and a significant percentage of high-grade lesions (88%). Alveolar soft part sarcoma, synovial, and epithelioid sarcomas also represent a major proportion of high-grade lesions and high

Table 2. LUNG METASTASES FROM SOFT TISSUE SARCOMA: INCIDENCE BY PRIMARY SITE FOR ALL PATIENTS WITH PULMONARY METASTASES

Primary Site	Total No. of Patients (%)	Patients With Lung Metastases (% of total)	% of All Lung Metastases
Extremity/trunk	1837 (58)	474 (26)	65
Retroperitoneal	466 (15)	63 (14)	9
Thoracic	193 (6)	44 (23)	6
Visceral-GI	206 (7)	12 (6)	2
Visceral-GYN	172 (6)	65 (38)	9
Visceral-GU	101 (3)	23 (23)	3
Head and neck	141 (5)	25 (18)	4
Skin/Others	33 (1)	13 (36)	2
Total	3149	719	100

Table 3. LUNG METASTASES FROM SOFT TISSUE SARCOMA: DISTRIBUTION BY HISTOLOGIC TYPE AND GRADE

Histology	Overall (% overall)	High-Grade Histology	% High-Grade	Patients With Lung Metastases	% Patients With Lung Metastases	% of All Patients With Lung Metastases
Alveolar soft part sarcoma	22 (0.7)	22	100	13	59	2
Embryonal rhabdomyosarcoma	97 (3.0)	97	100	25	26	3
Synovial sarcoma	225 (7.0)	215	96	98	44	14
Epithelioid	21 (1.0)	20	95	8	38	1
Spindle cell	56 (1.7)	51	91	20	36	3
Undifferentiated	25 (0.7)	22	88	15	60	2
Others*	221 (7.0)	190	86	65	29	9
Malignant peripheral nerve tumor	130 (4.0)	111	85	36	28	5
Leiomyosarcoma	590 (18.7)	492	83	149	25	21
Angiosarcoma	124 (3.9)	97	78	33	27	5
Malignant fibrous histiocytoma	559 (18.0)	376	67	132	24	18
Extraskeletal chondrosarcoma	57 (2.0)	32	56	18	32	2
Liposarcoma	657 (20.8)	329	50	86	13	12
Fibrosarcoma	314 (10.0)	15	16	19	6	3
Gastrointestinal stromal tumor	51 (2.0)	5	10	2	4	<1

* Includes adenosarcoma, anaplastic sarcoma, clear cell sarcoma, cystosarcoma, desmoplastic sarcoma.

rates of pulmonary metastases. One exception to this pattern is embryonal rhabdomyosarcoma. In this group of patients, all the primary tumors were of high grade; however, the rate of pulmonary metastasis was relatively low (26%). Liposarcoma has one of the lowest proportions of high-grade lesions and a correspondingly low rate of pulmonary metastases (13%). Fibrosarcoma also has a low incidence of high-grade histology (16%) and a low frequency of pulmonary metastases (6%).

Multivariate Analysis of Survival

Figure 1 depicts the overall disease-specific survival for all patients with lung metastases. The overall median survival was 15 months. The overall actuarial 3-year survival rate was 25%. For the 233 patients who were alive at the time of last follow-up, the median postmetastasis follow-up was 10.4 months. Surgical resection was the factor that had the greatest impact on survival after lung metastasis. Patients treated with resection had a median survival after complete resection of 33 months (Fig. 2). Their 3-year actuarial survival rate was 46%, with a 5-year actuarial survival rate of 37%. The patients who did not undergo resection had a median survival of 11 months and a 3-year actuarial survival rate of 17% (Fig. 2). Patients who underwent an incomplete resection had a median survival of 16 months, which represented a marginal statistical difference from patients treated with nonresectional therapy ($p = 0.05$). A complete resection was associated with a significant improvement in survival compared with an incomplete resection ($p = 0.003$).

One hundred thirty-eight patients underwent resection of pulmonary metastases before February 28, 1992. These patients represent potential postmetastasis 5-year survivors. Of this group, 20 patients (14%) were actual 5-year survivors and were alive at the time of last follow-up (Table 4). Of this group of long-term survivors, 13 (9%) were alive without evidence of disease. The longest survivor has undergone five thoracotomies and at last follow-up was alive without evidence of disease 19 years after her original thoracotomy. Seven patients are currently alive with dis-

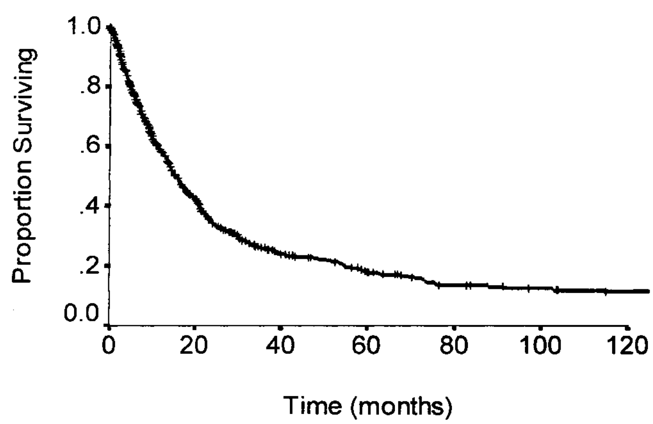

Figure 1. Overall disease-specific survival for patients with pulmonary metastases (n = 719). The median survival for all patients with lung metastasis is 15 months.

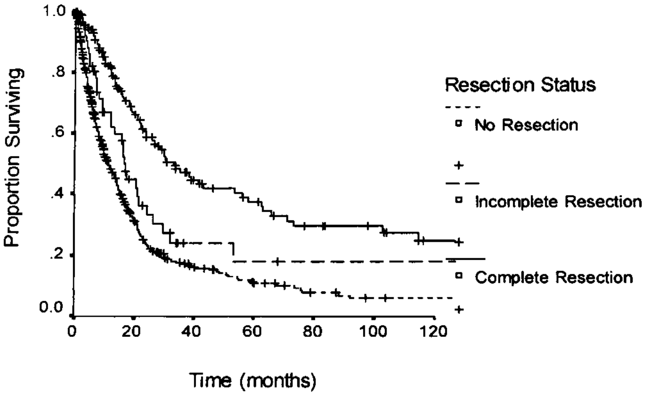

Figure 2. Kaplan-Meier plot of disease-specific survival for patients with pulmonary metastases, by treatment. Patients treated with complete resection (n = 161) had a median survival of 33 months. For patients who did not undergo resection (n = 473), the median survival was 11 months. For patients who underwent incomplete resection (n = 52), the median survival was 16 months ($p < 0.001$, complete resection *vs.* no resection or incomplete resection.)

ease. In 13 of the long-term survivors, recurrent pulmonary disease developed, and they were treated with repeated lung resection. The number of lung resections ranged from one to nine.

Clinical and tumor-related variables were analyzed as potential determinants of survival (Table 5). On univariate analysis, patient age 50 years or older was a significant predictor of negative outcome after the development of lung metastasis. After the development of pulmonary metastasis, patients with low-grade primary lesions had a more favorable prognosis than did patients with high-grade lesions.

The disease-free interval is the time between the treatment of the primary lesion and the diagnosis of metastatic disease. The median disease-free interval for all patients with pulmonary metastases was 10.3 months. The disease-free interval was examined as a prognostic factor. A disease-free interval of 1 year or less was a significant indicator of poor prognosis in a univariate analysis ($p < 0.001$).

Specific sites of primary disease were analyzed as potential determinants of survival (Table 5). Sarcomas arising in nonextremity locations appeared to have a slightly more favorable prognosis compared with extremity lesions ($p = 0.05$; Table 5). However, the difference in median survival was small. The most significant site-dependent factor was the presence of a gynecologic sarcoma as primary. The majority of these tumors were uterine leiomyosarcomas. Patients with pulmonary metastases from gynecologic visceral sarcomas had a median survival of 33.5 months. Patients with all other sarcomas with lung metastases had a median survival of 14.3 months. This survival advantage did not extend to other visceral sarcomas.

Histologic types were analyzed for their influence on survival. Patients with liposarcoma had a significantly worse prognosis than those with other histologic types. Median survival was 9.8 months for patients with liposarcoma, in contrast to 16 months for all other histologic sites. Patients with a malignant peripheral nerve tumor also had a less favorable prognosis. In contrast, leiomyosarcoma represented a favorable primary histology. Median postmetastasis survival in patients with leiomyosarcoma was 20 months *versus* 14 months in the nonleiomyosarcoma group.

Table 4. LONG-TERM SURVIVORS AFTER COMPLETE RESECTION

Patient	Sex	Grade	Histology	Depth	Site	Number of Lung Resections	Status	Follow-Up (months)
1	F	High	Leiomyosarcoma	Deep	Uterus	3	AWD	61
2	F	Low	Fibrosarcoma	Deep	Kidney	2	NED	63
3	M	Low	Fibrosarcoma	Deep	Neck	4	NED	67
4	F	High	Leiomyosarcoma	Deep	Uterus	5	AWD	68
5	M	High	Hemangiopericytoma	Deep	Thigh	1	NED	77
6	F	High	Fibrosarcoma	Deep	Lower leg	—	AWD	83
7	M	High	MFH	Deep	Pelvis	1	NED	84
8	F	High	Synovial sarcoma	Deep	Thigh	2	NED	87
9	M	High	Epithelioid	Deep	Buttock	5	NED	91
10	F	High	Lymphangiosarcoma	Deep	Elbow	2	NED	115
11	M	High	Chondrosarcoma	Deep	Knee	2	NED	120
12	M	High	Synovial sarcoma	Deep	Shoulder	—	NED	124
13	F	High	Leiomyosarcoma	Deep	Uterus	2	NED	125
14	M	High	MFH	Deep	Thigh	—	NED	139
15	M	High	Synovial	Deep	Thigh	2	AWD	145
16	F	High	Synovial	Deep	Wrist	9	AWD	147
17	F	High	Alveolar soft part	Deep	Thigh	8	NED	147
18	F	Low	Leiomyosarcoma	Deep	Uterus	1	AWD	150
19	M	High	Embryonal rhabdo.	Deep	Testis	—	NED	153
20	F	High	Leiomyosarcoma	Deep	Uterus	5	NED	234

MFH, malignant fibrous histiocytoma; AWD, alive with disease; NED, no evidence of disease.

Table 5. UNIVARIATE ANALYSIS OF SURVIVAL: PATIENTS WITH PULMONARY METASTASES FROM SOFT TISSUE SARCOMA

Variable	n	Median Survival (months)	p (log-rank)
Age			
<50	353	16.7	0.016
≥50	366	13.4	
Gender			
Female	352	16.4	0.22
Male	367	14.5	
Grade			
High	645	14.5	0.05
Low	71	22.6	
Unknown	3		
Disease-free interval			
<12 months	383	12.4	<0.001
≥12 months	336	18.4	
Local recurrence			
No	558	14.8	0.50
Yes	161	15.7	
Resection			
No resection	473	11.2	<0.001
Incomplete	52	16.4	
Complete	161	33.5	
Unknown	33		
Extremity primary			
Extremity	409	14.3	0.05
Non-extremity	310	16.5	
Visceral Primary*			
Visceral	41	15.4	0.97
Non-visceral	678	14.9	
Gynecologic visceral primary			
Gynecologic visceral	66	33.5	<0.001
Others	653	14.3	
Retroperitoneal primary			
Retroperitoneal	63	12.4	0.71
Others	656	15.4	
Truncal primary			
Truncal	110	16.5	0.85
Others	609	14.8	
Primary histology			
MFH	132	13.6	0.23
Non-MFH	587	15.4	
Liposarcoma	86	9.8	<0.001
Non-liposarcoma	633	16.1	
Fibrosarcoma	19	21.2	0.09
Non-fibrosarcoma	700	14.7	
Angiosarcoma	33	14.1	0.32
Non-angiosarcoma	686	15.4	
Emb. Rhabdo.	694	15.6	0.56
Non-ER	25	15.4	
MPNT	36	7.7	0.005
Non-MPNT	683	15.4	
Leiomyosarcoma	149	20.1	0.02
Non-leiomyosarcoma	570	14.3	
Synovial	99	17.0	0.57
Non-synovial	620	14.5	
Number of metastases resected			
<4	117	30.0	0.67
≥4	85	21.5	
Laterality of metastases resected			
Bilateral	114	23.3	0.11
Unilateral	114	35	

* Excludes gynecologic visceral primaries.
MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral nerve tumor.

Table 6. MULTIVARIATE ANALYSIS OF SURVIVAL: PATIENTS WITH PULMONARY METASTASES FROM SOFT TISSUE SARCOMA

Variable	Cox Model p Value	Relative Risk (95% CI)	Prognostic Significance
Resection	<0.0001	0.51 (0.43–0.63)	Favorable
Disease-free interval >12 mo.	0.0006	0.71 (0.59–0.86)	Favorable
Low-grade primary tumor	0.02	0.66 (0.46–0.95)	Favorable
Liposarcoma	0.0003	1.71 (1.25–2.16)	Unfavorable
Age ≥50	0.008	1.30 (1.05–1.54)	Unfavorable
Malignant peripheral nerve tumor	0.03	1.50 (1.04–2.29)	Unfavorable
Extremity	0.28		
Gynecologic visceral	0.21		
Leiomyosarcoma	0.58		

Other than complete resection, the technical details of the surgical procedure did not appear to provide significant prognostic information. Patients with less than four metastases had a survival modestly better than patients with four or more lesions, but this did not reach significance. Patients with unilateral metastases also had a slightly more favorable survival, although again this was not statistically significant.

For multivariate analysis, all potentially significant factors were entered into a Cox proportional hazards model (Table 6). In the Cox model, surgical resection remained the most significant predictor of postmetastasis survival. A disease-free interval of >12 months was also a favorable prognostic factor. Patients with a primary tumor classified as low grade also had a more favorable survival.

Cox model analysis demonstrated that two histologic variants were independent prognostic factors for survival after pulmonary metastasis. Liposarcoma was a predictor of poor prognosis: the relative risk of death from pulmonary metastatic disease from liposarcoma was 1.73. Malignant peripheral nerve tumor was also associated with an increased relative risk of dying from metastatic sarcoma. Patient age of 50 years or older also represented an independent predictor of diminished survival after the development of pulmonary metastasis. Although distant metastases are uncommon in patients with a histologically low-grade primary tumor, patients who did develop metastases had a more favorable prognosis in this multivariate analysis. Gynecologic visceral primaries were associated with a favorable survival in the univariate analysis, but this did not prove to be significant in the multivariate analysis. Additional factors such as an extremity location of the primary and a histologic diagnosis of leiomyosarcoma were no longer significant on multivariate analysis.

DISCUSSION

This series represents a large, single-institution experience with pulmonary metastases from soft tissue sarcoma. Previous work from our institution detailed the development and treatment of lung metastases in patients with primary extremity sarcoma.[2] The current report profiles the spectrum of pulmonary metastases in sarcoma, encompassing all primary sites as well as most histologic variants.

The distribution of primary disease sites among patients with pulmonary metastases indicates that the majority of pulmonary metastases arise from extremity primaries. These data also indicate that sarcoma arising in any anatomic location has the capacity to metastasize to the lungs (Table 2). The analysis of patients with primary disease treated at MSKCC provides the most unbiased representation of the incidence of pulmonary metastases for each anatomic site. Analysis of all patients with pulmonary metastasis treated at MSKCC demonstrates a significant number of patients with pulmonary metastases from primary visceral sarcoma. However, this appears to be related to the fact that patients' local physicians treat the major portion of primary visceral sarcomas, particularly uterine sarcoma. Patients are subsequently referred to a cancer center when they are diagnosed with pulmonary metastases.

Analysis of the histology of the primary lesions indicates that pulmonary metastases arise most commonly in patients with malignant fibrous histiocytoma, synovial sarcoma, liposarcoma, and leiomyosarcoma. A variety of other histologic variants, which are primarily high-grade lesions, have a higher incidence of pulmonary metastasis. Because most of these are unusual forms of sarcoma, such as undifferentiated sarcoma, and alveolar soft part sarcoma, their contribution to the total number of patients with pulmonary metastasis is low.

The survival benefit associated with resection of pulmonary metastatic disease appears to be significant. Patients who underwent at least one complete pulmonary resection had a median survival of 33 months and a 3-year actuarial survival rate of 46%. The actuarial 5-year survival rate was 37%. Patients who did not undergo resection had a median survival of 11 months and a 3-year actuarial survival rate of 17%. A previous report from our institution examined survival in patients with pulmonary metastases from primary extremity sarcoma.[2] The median survival after resection in these patients was 19 months. In our current analysis, the median survival of patients with extremity sarcoma with lung metastasis was 30 months. There are several features of the current analysis that produce this variation. Because in the current series we attempted to include as many patients as possible for analysis of prognostic factors, the median follow-up period was quite short (10.4 months for survivors). The prior series from our institution had a significantly greater follow-up interval (30 months for survivors).

To obtain more complete follow-up and to analyze patients similar to those in the previous series, we reviewed postmetastasis survival in patients with extremity sarcoma who had undergone pulmonary metastasectomy before February 28, 1992. This group consisted of 92 patients with a median postmetastasis survival of 21 months and a median follow-up of 18 months. The median follow-up for survivors in this group was 78 months. Patients within this group who had undergone a complete resection had a median survival of 24 months. These data suggest that the duration of follow-up is critical in interpreting survival in these patients. It would appear that the median survival of 33 months reported in our current series is a generous estimate, and a median survival of 19 to 24 months, which was seen in earlier series, is more likely.

Although long-term survival is possible after complete resection, in most patients recurrent disease develops (see Table 4). In patients who underwent resection and who were potential 5-year survivors, there were 20 actual survivors. As such, the actual 5-year survival rate in this series was 14% (20/138). In this series, recurrent disease developed in 13 of the long-term survivors and was treated with at least one additional resection. The number of pulmonary resections in this group of patients ranged from one to nine. Thirteen patients were alive without evidence of disease 5 or more years after their original lung resection for pulmonary metastases. These data suggest that pulmonary metastases frequently represent diffuse involvement of the lung parenchyma. As such, it is difficult to eradicate all foci of metastatic disease with resection. Long-term survivors appear to belong to a subset of patients with indolent, lung-only disease. It is possible to control disease in these patients for an extended period with repeated pulmonary resection. Other groups have also documented the safety and utility of repeated pulmonary resections.[15]

Series from other institutions have focused on survival patterns after resection of lung metastases. In a review of 68 patients treated at the National Cancer Institute, the overall 3-year survival rate was 28%, with a 35% 3-year survival rate for patients who underwent complete resection. Patients in this series who underwent incomplete resection had a median survival of 9 months.[6] More favorable survival was described in a multiinstitutional European study.[16] These authors reviewed the collective experience from 11 hospitals involving 255 patients who underwent resection of pulmonary metastases. They reported an overall survival rate of 54% at 3 years and 38% at 5 years. Other centers have demonstrated 5-year survival rates ranging from 21% to 25%.[4,9]

Prognostic Factors

A variety of prognostic factors have been reviewed in a number of different series. The ability to resect metastatic disease completely is consistently the most significant factor in determining postmetastasis survival. An extended disease-free interval has also been demonstrated by a number of groups as a positive predictor of survival.[9,10]

Because the current study encompassed significant numbers of patients with metastases from a complete array of histologic types and primary anatomic locations, we sought to determine if any of these features demonstrated prognostic significance. Prior series have not consistently demonstrated prognostic significance for histology in metastatic soft tissue sarcoma.[6,9] One report indicated poor prognosis associated with unclassified sarcomas and a more favorable prognosis for malignant fibrous histiocytoma.[4] In the current series, patients with liposarcoma had a diminished postmetastasis survival when compared with those with other histologies. The median survival of all patients with liposarcoma and lung metastases was 11 months (Table 4). The poor prognosis associated with liposarcoma may be related to the fact that pleomorphic, high-grade myxoid subtypes of liposarcoma are more often associated with the development of pulmonary metastases than low-grade myxoid or well-differentiated subtypes.[17] Patients with malignant peripheral nerve tumors also have an unfavorable prognosis, although this is less significant than liposarcoma. In multivariate analysis, both histologies are independent predictors of diminished postmetastasis survival.

Previous work has also not consistently demonstrated a relation between primary site and survival.[9,16] One author reported a more favorable prognosis for primary lesions arising in the trunk.[11] In the current series, univariate analysis demonstrated increased survival for patients with gynecologic visceral primaries and nonextremity primaries. On multivariate analysis, however, neither gynecologic visceral tumors nor nonextremity tumors proved to be significant prognostic factors.

We also examined the number of nodules resected as well as the presence of unilateral *versus* bilateral metastatic disease as prognostic factors. Two large series indicated a prognostic significance associated with the number of nodules resected. Casson et al[4] demonstrated that patients with three or fewer nodules on preoperative lung tomograms had a significantly longer survival than patients with four or more nodules. Similar findings were noted by Putnam et al.[5] They found that patients with four or fewer nodules resected at operation have a longer postthoracotomy survival than patients with more than four nodules. The same group demonstrated that unilateral *versus* bilateral disease is not a significant indicator of prognosis. The current study also indicated that bilateral disease is not an independent negative predictor of survival. In our study, however, the number of nodules was not a significant prognostic factor. As long as the pulmonary metastases were completely resected, there was no significant difference between patients who had less than or more than four lesions resected.

Most pulmonary metastases arise from high-grade primary tumors. In this series, however, lung metastases developed from low-grade tumors in a subset of patients. Because these lesions have demonstrated the capacity to metastasize, their biologic behavior is more consistent with high-grade lesions. The postmetastasis survival in this group of patients has not been well studied. The European multiinstitutional review demonstrated a more favorable survival for patients with low-grade lesions.[16] In the current series, we also found a modest survival advantage for patients with a low-grade histology. Although these lesions demonstrate a metastatic potential similar to that of high-grade tumors, they appear to have a more indolent rate of disease progression, which may be related to a survival advantage.

A variety of previous groups demonstrated the significance of the disease-free interval in determining postresection survival.[4–6] The current study supported these findings. Disease-free interval appears to serve as an indicator of the overall tempo of disease progression. Patients in whom recurrence develops after a brief disease-free interval have a tumor that is biologically aggressive, and these patients generally have a less favorable postmetastasis survival.

CONCLUSION

Long-term survival is possible after resection of pulmonary metastases from soft tissue sarcoma. Unfortunately, recurrent disease develops in a significant number of patients. Of the 20 long-term survivors in this study, recurrent disease developed in 13, who underwent repeat pulmonary resection. Patients in whom metastatic disease develops after a disease-free interval of >1 year and can be completely resected are most the likely to be long-term survivors. Patients with pulmonary metastases from liposarcoma and malignant peripheral nerve tumors are less likely to be long-term survivors. Given the continued paucity of meaningful therapeutic alternatives, surgical excision, when at all possible, should remain the treatment of choice for metastatic soft tissue sarcoma to the lung.

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References

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. CA Cancer J Clin 1998; 48(1):6–29.
2. Gadd MA, Casper ES, Woodruff JM, et al. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma [see comments]. Ann Surg 1993; 218(6):705–712.
3. Lewis JJ, Brennan MF. Soft tissue sarcomas. Curr Probl Surg 1996; 33(10):817–872.
4. Casson AG, Putnam JB, Natarajan G, et al. Five-year survival after pulmonary metastasectomy for adult soft tissue sarcoma. Cancer 1992; 69(3):662–668.
5. Putnam JB Jr, Roth JA, Wesley MN, et al. Analysis of prognostic factors in patients undergoing resection of pulmonary metastases from soft tissue sarcomas. J Thorac Cardiovasc Surg 1984; 87(2):260–268.
6. Jablons D, Steinberg SM, Roth J, et al. Metastasectomy for soft tissue sarcoma. Further evidence for efficacy and prognostic indicators. J Thorac Cardiovasc Surg 1989; 97(5):695–705.
7. Lanza LA, Putnam JB Jr, Benjamin RS, Roth JA. Response to chemotherapy does not predict survival after resection of sarcomatous pulmonary metastases. Ann Thorac Surg 1991; 51(2):219–224.
8. Casper ES, Gaynor JJ, Harrison LB, et al. Preoperative and postoperative adjuvant combination chemotherapy for adults with high-grade soft tissue sarcoma. Cancer 1994; 73(6):1644–1651.
9. Verazin GT, Warneke JA, Driscoll DL, et al. Resection of lung metastases from soft-tissue sarcomas. A multivariate analysis. Arch Surg 1992; 127(12):1407–1411.
10. van Geel AN, van Coevorden F, Blankensteijn JD, et al. Surgical treatment of pulmonary metastases from soft tissue sarcomas: a retrospective study in The Netherlands. J Surg Oncol 1994; 56(3):172–177.
11. Creagan ET, Fleming TR, Edmonson JH, Pairolero PC. Pulmonary resection for metastatic nonosteogenic sarcoma. Cancer 1979; 44(5): 1908–1912.
12. Vezeridis MP, Moore R, Karakousis CP. Metastatic patterns in soft-tissue sarcomas. Arch Surg 1983; 118(8):915–918.
13. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–462.
14. Cox D. Regression models and life tables. J Royal Stat Soc 1972; 34:187–220.
15. van Geel AN, Hoekstra HJ, van Coevorden F, et al. Repeated resection of recurrent pulmonary metastatic soft tissue sarcoma. Eur J Surg Oncol 1994; 20(4):436–440.
16. van Geel AN, Pastorino U, Jauch KW, et al. Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. Cancer 1996; 77(4):675–682.
17. Chang HR, Gaynor J, Tan C, et al. Multifactorial analysis of survival in primary extremity liposarcoma. World J Surg 1990; 14(5):610–618.

Discussion

Dr. Marshall M. Urist (Birmingham, Alabama): President Griffen, Secretary Copeland, Members and Guests. Dr. Brennan and his colleagues from Memorial Sloan-Kettering Cancer Center continue to make outstanding contributions to our understanding of the natural history and the treatment of soft tissue sarcomas.

Their prospective database of over 3,000 patients provides a very powerful tool to analyze the results of these treatments. They confirm for us that complete resection of the primary tumor is the best way to get any long-term survival in this patient population. They also confirm other reports in the literature, but used much greater numbers to do that. And they show us the safety and the value of multiple thoracotomies to prolong this effect which is achieved in, unfortunately, such a small proportion of patients.

Their follow-up is relatively short, but the effect is also seen in a relatively short period of time. So the continued analysis of this database will solidify these numbers. As is shown in the manuscript though, this is an actuarial survival, so we are going to ask to look for the actual survival of these patients as we follow this patient population.

The questions that I would ask are, first of all, related to the method of detection. If the limitation of this procedure is related to the inability to completely resect the tumor, what is the best way to preoperatively evaluate this? Is the use of thoracoscopy helpful? What are the intraoperative findings that prevent one in achieving this goal?

Dr. Brennan also mentioned about adjuvant therapy and the failure of adjuvant therapy to show any benefit in this patient population. I'd like to ask him, what is the current status of adjuvant therapy for patients who undergo pulmonary resection? And is there any role for treating patients outside of a prospective protocol looking at this situation? I know that we all hear from our medical oncologists regularly about how they want to add therapy to this overall favorable risk situation that we've created after resection of metastases.

Since the lung itself is the most common site of failure, is additional therapy at that site, intensified therapy, that is, is pulmonary perfusion going to show any benefit in this patient population?

DR. JEFFREY A. NORTON (San Francisco, California): Thank you very much. I, too, rise to say that this was an outstanding paper. My questions really are more pragmatic.

First of all, how would you follow patients with extremity sarcomas postoperatively in light of the development of pulmonary metastases? When do you recommend CT and how often? And how does that vary with a patient who has a lower probability of developing pulmonary metastases, for example, a GI stromal tumor or a retroperitoneal sarcoma?

A related question is, what's the incidence of false positive pulmonary metastases on CT or other studies in your experience?

You didn't mention how metastases you would resect. In other words, what's the maximum number of metastases that you would resect? And you used wide variety of approaches to resect these metastases. Which do you actually favor?

In my experience when I was at NCI, I think we commonly did median sternotomy and explored such that we found other metastases that were missed on CT. And I wondered how often, for example, you have additional metastases which would warrant a bigger surgical approach like median sternotomy.

And I had a similar question like Dr. Urist about chemotherapy. But my question is, is there any role for chemotherapy in your opinion for high-grade sarcomas or any sarcoma? When do you actually use chemotherapy? And if you recommend using it, what drugs do you use?

DR. JOHN S. BOLTON (New Orleans, Louisiana): I'd just like to second Dr. Urist's compliments—it's a tremendous paper. And I'd also like to address several questions to Dr. Brennan.

The actuarial 5-year survival for those completely resected in your study was 37% in keeping with other reports, but the actual 5-year survival for those resected prior to 1992 was only 14%. And I just would like you to amplify or discuss further that discrepancy. Are we perhaps not doing quite as well with this therapy as we have thought over the past decade?

Secondly, given the fact that patients who have unilateral disease on preoperative CT scan, 35% to 40% are found to have bilateral disease if median sternotomy and bilateral exploration is done. And among patients who have thoracoscopic resections — who have CT-directed VATs, or video assisted thoracoscopic resection, and then undergo immediate open resection, over 50% of patients in a study from your own institution have additional disease.

One problem in this disease, I think, is what you don't see on the CT scan. And do you really feel that thoracoscopic resection is a viable option at this point in time?

And a final question. It's implied in the manuscript, I think, that most patients ultimately fail in the lungs. But can you provide a bit more detail about that? How many patients ultimately actually die because of their lung metastases, and how many die because of disease outside of the lung?

DR. MURRAY F. BRENNAN (Closing Discussion): Thank you, Mr. Chairman. Dr. Urist asked about the methods of detection. Predominately, of course, that is by chest x-ray. A suspicious chest x-ray warrants a CT scan.

He asked about the intraoperative findings. As he's well aware, the majority of patients will have more lesions identified than seen on the CT. The problem, of course, is that if you take a plain chest x-ray, identify lesions to a CT scan, you'll at least double the number of identified lesions on the CT scan. But only half of those will be malignant. So there's an increased sensitivity, but there is a decreased specificity.

Dr. Urist also asked about adjuvant treatment. We would suggest that these patients only enter into a prospective control. That's not easy to do. Most medical oncologists believe sarcomas to be responsive lesions, and many of them get treated. I don't believe that's of value.

Our current approach is developing immune adjuvants, trying to look at ways in which we can provoke a patient response to known antigens expressed on the surface of sarcoma much as has been done with melanoma. It's interesting that the surface gangliocytes are in fact expressed more commonly on sarcoma than they are on melanoma. And those have been previously shown by us and others to predict outcome if there's immune response, and we are pursuing that approach.

Dr. Norton asked about the follow-up. I think the only clues that you can have, of course, is 80% of the high-grade lesions will recur within 2 years, so that's the time of more intense follow-up. Low-grade tumors are uncommon and unlikely to have pulmonary new metastasis and so can be followed, I believe, with chest x-ray.

And as you pointed out, the GI stromal tumors are rare to be revealed in lung. In addition, of course, the GI stromal tumor, 80% of those will present with metastasis to the liver. There are false positives, as I commented in answering Dr. Urist's question.

How many lesions will we resect? Well, I wish Michael Burt was here to tell me what his record was. I think it was very significant. The philosophy, of course, is only complete resection matters. And that's true of every known metastasis that undergoes resection that I'm aware of. It's absolutely true in liver; it's absolutely true for lung for other histopathologies. The complete gross resection is the only factor that translates into long-term survival, not the actual number.

He asked about the technical approaches in terms of median sternotomy Clamshell, and Dr. Bolton asked about VATs. Obviously, I am not the person doing the pulmonary resections. The majority, I think, would now undergo a Clamshell operation. There are technical difficulties as many of the thoracic surgeons know in the audience from trying to get access to the posterior aspect of the lung through median sternotomy alone. And some of our surgeons still continue to favor stage thoracotomies. Clearly, with only unilateral disease on CT scan, unilateral thoracotomy would be approached.

Dr. Bolton, I think, is correct that the VATs has a limited application in most metastatic disease above and beyond making the diagnosis. The ability to completely resect someone with video-assisted thoracoscopic surgery in someone who has metastatic disease is low. And as Dr. Bolton pointed out, we have shown in another prospective trial that when a VATs is applied and then you open those patients, that you double the number of identified metastases that would be found purely by palpation alone.

Finally, Dr. Bolton and Norton both asked about chemotherapy. It's my personal opinion that these people should only receive chemotherapy in an adjuvant—in a prospective randomized trial. That's difficult to do. I'm cautiously optimistic that the American College of Surgeons oncology group will allow us to answer that group by having surgeons entering the patients.

And, Dr. Bolton, you're absolutely right, although it is a database that extends over 15 years, the long-term benefit is clearly not 37% for all patients and is much closer to 20% in actual survival benefit. But in the absence of any other effective therapy, I believe it is worth pursuing at least in the context of the trial.